

IN THE UNITED STATES DISTRICT COURT  
FOR THE WESTERN DISTRICT OF WISCONSIN

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DSM IP ASSETS, B.V. & DSM BIO-BASED  
PRODUCTS & SERVICES, B.V.,

Plaintiffs and Counter-Defendants

v.

LALLEMAND SPECIALTIES, INC. &  
MASCOMA LLC,

Defendants and Counterclaimants.

OPINION & ORDER

16-cv-497-wmc

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In this lawsuit, plaintiffs DSM IP Assets, B.V. and DSM Bio-Based Products & Services B.V. (collectively “DSM”) claim that Lallemand Specialties, Inc. and Mascoma LLC (collectively “Lallemand”) are infringing U.S. Patent No. 8,795,998 (the “’998 patent”). Before the court are the parties’ cross motions for claims construction and summary judgment, with plaintiffs seeking summary judgment on defendants’ anticipation defense, and defendants seeking summary judgment on their indefiniteness defense and plaintiffs’ claim of infringement. (*See* dks. ##59, 72, 64.) The court held an “expert colloquy” on Friday March 16, 2018, at which the parties’ experts made brief presentations and were guided through a discussion with the court’s neutral expert (*see* dkt. #144) regarding proposed claim constructions (dkt. #151) and the issues before the court at summary judgment, followed by cross-examination by the parties’ counsel. Having considered the parties’ extensive written submissions, expert reports and colloquy presentations, along with additional argument of counsel and the record as a whole, the court will now issue its final claims constructions, grant plaintiffs summary judgment on anticipation and indefiniteness, and deny defendants’ motion for summary judgment on infringement.

## UNDISPUTED FACTS<sup>1</sup>

### A. Parties

Plaintiffs are Netherlands corporations that have their registered places of business in The Netherlands. DSM Bio-Based Products & Services is a “pioneer” “in biomass conversion” and develops “bioconversion technologies” for the “biofuels industry.” 2017 Review of Business, DSM, [http://annualreport.dsm.com/ar2017/en\\_US/7-3-innovation-center.html#H4794108691](http://annualreport.dsm.com/ar2017/en_US/7-3-innovation-center.html#H4794108691) (last visited Mar. 13, 2018). DSM IP Assets, B.V. is the holding company for DSM’s intellectual property. Lallemand is a Minnesota corporation that has its principal place of business in Milwaukee, Wisconsin, while Mascoma is a Delaware LLC, with its principal place of business in Lebanon, New Hampshire. Lallemand “specializ[es] in the development, production, and marketing of yeasts and bacteria,” while Mascoma is “a leader in advanced bioconversion products.” *See At a Glance*, Lallemand, <http://www.lallemand.com/about-us/at-a-glance/> (last visited Mar. 13, 2018); *Overview*, Mascoma, <http://www.mascoma.com/about-us/overview/> (last visited Mar. 13, 2018).

### B. Enzymatic Activity

A chemical agent that increases the rate of reaction without being consumed by the reaction is a catalyst. Enzymes are the most common biological catalysts. The rate at which a

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<sup>1</sup> The following facts are material and undisputed for purposes of summary judgment except where specifically noted.

reaction produces its end product is the rate of catalysis.<sup>2</sup> (Defs.’ Resp. to Pls.’ PFOF (dkt. #80) ¶ 21.) The rate of catalysis of an enzymatic reaction can be impacted by various conditions, including “changes in the concentration of substrate, enzyme, and/or other molecules that can bind to enzymes, pH, and temperature, and other cellular mechanisms.” (*Id.* ¶ 22.) For instance, increasing the concentration of substrate increases the reaction rate of an enzyme-catalyzed reaction until it reaches the saturation level.

Cells modify specific enzyme activity based on the cell’s production needs through allosteric regulation, covalent modification of enzyme structure, and inhibition. A cell’s production of enzymes involves the expression of genes and then translation into an active enzyme. While genetic expression produces enzymes, their activity is not solely dependent on expression. After an enzyme is produced, it can be modified by chemical reactions such as thiolation, methylation, phosphorylation, and acetylation. Enzymes can also be impacted by temperature and pH. For instance, each enzyme has a specific pH at which it operates most efficiently; the optimal pH depends on ionizable amino acid residues. The enzyme can become denatured by a change away from its optimal pH due to changes in the amino acids’ ionization states. As for temperatures, from 0°C to approximately 40°C, enzymatic reaction rates tend to double for every 10°C increase in temperature, but at some point increasing temperature causes denaturation of enzymes, decreasing the reaction rate. (*See* Pls.’ Reply to Defs.’ Resp. to Pls.’ PFOF (dkt. #92) ¶¶ 25-26, 28-30, 87-90.)

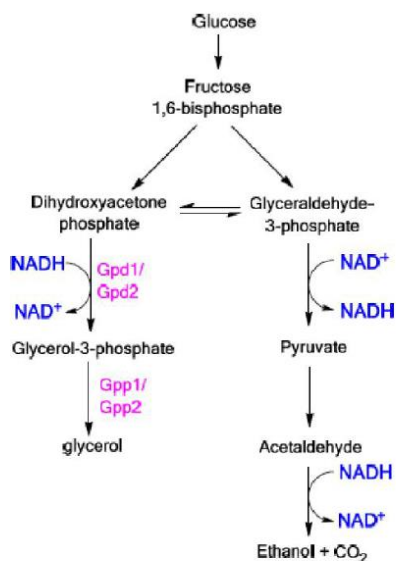
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<sup>2</sup> Defendant Lallemand does not dispute that the rate of catalysis is the rate at which the product of the reaction is formed, although it disputes that the Russell text cited by plaintiff DSM equates enzymatic activity to the rate of catalysis. (Defs.’ Resp. to Pls.’ PFOF (dkt. #80) ¶ 21.) For reasons discussed in this opinion, the court views the definitions as equivalent, except that “enzymatic activity” in the patent could also be measured as the rate at which the substrate of the reaction is consumed.

The Nomenclature Committee of the International Union of Biochemistry and Molecular Biology assigns “EC” numbers, which categorize enzymes based on the reactions they catalyze. For example, one of the principle enzymes at issue here is categorized as “EC 1.2.1.10,” which refers to the catalysis of the conversion of acetyl-Coenzyme A to acetaldehyde; an enzyme that performs this task is also referred to as NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase activity.

### C. Ethanol Production

The largest industrial biotechnology fermentation process is ethanol production. The parties agree that *Saccharomyces cerevisiae*, a species of yeast, produces ethanol by fermenting glucose obtained from raw material, like corn, as illustrated here:<sup>3</sup>



In the production of ethanol, the NADH created by the conversion of glyceraldehyde-3-phosphate to pyruvate is used in the creation of ethanol from acetaldehyde. Where redox imbalance exists (i.e., where there is excess NADH), cell growth and ethanol production are impeded. Thus, yeast cells also produce glycerol to consume unused NADH as the main pathway for intracellular redox balance. In that reaction,

dihydroxyacetone phosphate (“DHAP”) is reduced to glycerol-3-phosphate (“G-3-P”) via

<sup>3</sup> (See Pls.’ Resp. to Defs.’ PFOF (dkt. #75) ¶ 17 (citing Stephanopoulos Infringement Rpt. (dkt. #47) ¶ 16).) Among other simplifications, the actual reaction between glucose and pyruvate is simplified in this diagram. For a more detailed depiction of the reaction, see *Glycolysis*, Wikipedia, <https://en.wikipedia.org/wiki/Glycolysis> (last visited Mar. 22, 2018).

NAD<sup>+</sup>-dependent glycerol-3-phosphate dehydrogenase (“GPD”), which involves oxidizing NADH into NAD<sup>+</sup>.<sup>4</sup> The G-3-P is hydrolyzed creating glycerol and inorganic phosphate by glycerol 3-phosphate phosphatase (“GPP”).<sup>5</sup>

Importantly, glycerol is considered a waste byproduct of ethanol production because it uses some of the glucose that could go toward additional ethanol production. This is no small problem because in industrial-scale ethanol production, glycerol production can decrease ethanol yield by millions of gallons. At the colloquy, the experts agreed that for a yeast cell under anaerobic conditions, eliminating GPD2 would decrease -- but not eliminate -- glycerol production compared to a yeast cell with GPD2, all other things being equal.

#### **D. The '998 Patent**

##### **1. Overview and Prosecution History**

The '998 patent, entitled “Fermentative Glycerol-Free Ethanol Production,” was filed July 18, 2011 and issued on August 5, 2014. The listed inventors are Jacobus Thomas Pronk, Antonius Jeroen Adriaan Van Maris, and Victor Gabriel Guadalupe Medina. The only assignee listed is Technische Universiteit Delft.

In response to an Office Action, the patent applicants explained that the invention “provides a yeast cell that actually grows preferentially in the presence of acetate,” which was unique because the prior art did not suggest modifying a yeast cell to make it a net consumer

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<sup>4</sup> There are two forms of the catalyst, GPD: GPD1 and GPD2, both of which trigger the same reaction in glycerol synthesis and are functionally equivalent (meaning they catalyze the same reaction at the same rate). Yeast cells express GPD1 when under osmotic stress to increase glycerol production; GPD2 is expressed under anaerobic conditions. GPD is needed for the conversion of DHAP to G-3-P.

<sup>5</sup> Just like GPD, the catalyst GPP has two isoforms: GPP1 and GPP2. GPP1 is expressed under conditions of anaerobic stress, while GPP2 is expressed under osmotic stress.

of acetate so that it could use “acetate as an electron acceptor to reoxidize NADH,” thereby reducing the necessity of glycerol synthesis. (May 2, 2013 Amend. & Resp. to Office Action (dkt. #62-12) 8.) These features, the applicants argued, distinguished the claimed invention from Valadi’s work by taking “advantage of the presence of acetate,” while “the Valadi yeast still generates the undesired acetate contaminant as a product of its metabolism.” (*Id.*) Unlike Valadi, which diminished the NADH-dependent glycerol synthesis, the claimed invention consumed acetate and supplied NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase -- an alternate NAD<sup>+</sup> generation pathway. (*Id.* at 10.) Further, the applicant explained that

Sonderegger, as is recognized by the Examiner, is focused on the phosphoketolase circuit that is an alternate route for pentose-based metabolism. The phosphoketolase pathway generates acetyl phosphate and thus it is necessary to employ both phosphotransacetylase as well as acetyl acetaldehyde dehydrogenase to generate NAD<sup>+</sup>. This approach is dependent on a pentose metabolism pathway, unlike the present invention, and it depends on acetate generated by the metabolism of xylose, and does not address the presence of acetate from external sources.

(*Id.* at 8.) The examiner found this explanation “persuasive” for claim 7, which became term 4 in claim 1. (*See* Aug. 1, 2013 Office Action (dkt. #47-74) 49); Oct. 30, 2013 Amend. (dkt. #47-75) 3-6; Not. Allowability (dkt. #47-75) 17-18.)<sup>6</sup>

## **2. Objectives and Specifications**

### **a. The Claimed Yeast Cells**

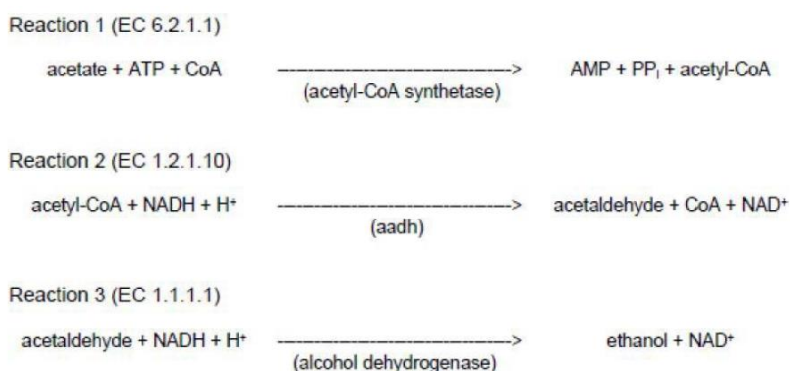
The patent at issue discloses transgenic yeast cells that reduce or completely lack

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<sup>6</sup> The parties agree that the appropriate timeframe for construction of the patent is July 24, 2009, but dispute four terms, all found in claim 1, as laid out and discussed in this court’s earlier order proposing claims construction (Proposed Claim Constructions (dkt. #151)), as well as the final claims constructions discussed *infra*.

“enzymatic activity needed for the NADH-dependent glycerol synthesis” as compared to wild-type yeast cells. (’998 Patent (dkt. #1-1) 2 (Abstract).) Specifically, the yeast cells either reduce or eliminate the activity of GPD or GPP. (*See id.* at 40 (67:20-28).) The cells also contain acetylating acetaldehyde dehydrogenase activity (EC 1.2.1.10), alcohol dehydrogenase (EC 1.1.1.1) and acetyl-Coenzyme A synthetase (EC 6.2.1.1), permitting the conversion of NADH to NAD<sup>+</sup>, which provides a metabolic pathway that complements the deletion of glycerol synthesis. Thus, the patent provides two methods of reducing NADH-dependent glycerol synthesis.

The claimed transgenic yeast cells convert acetate or acetic acid into ethanol through three different, enzymatic reactions using acetyl-CoA synthetase (EC 6.2.1.1), aadh (EC 1.2.1.10), or alcohol dehydrogenase (EC 1.1.1.1):<sup>7</sup>



The patent specifies aldehyde/alcohol dehydrogenase enzyme (“AdhE”) as a “bifunctional protein” that performs EC 1.2.1.10 activity from *Escherichia coli*, *Staphylococcus aureus* and *Piromyces* sp.E2. A bifunctional protein is one that catalyzes two reactions.

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<sup>7</sup> (*See* Defs.’ Reply to Pls.’ Resp. to Defs.’ PFOF (dkt. #95) ¶ 39 (citing Winge Infringement Report (dkt. #51) ¶ 19).)

### **b. Blomberg Assay & HPLC Analysis**

At the heart of defendants' request for summary judgment on indefiniteness is the Blomberg assay. In the section titled Enzyme Activity Assays, the patent details that "Glycerol-3-phosphate dehydrogenase activities were assayed in cell extracts at 30° C. as described previously (Blomberg and Adler (1989), J. Bacteriol. 171:1087-1092.[.])]" ('998 Patent (dkt. #1-1) 16 (20:37-40.)). The Blomberg assay is used to measure GPD activity through the measurement of substrate consumption. At the colloquy, the experts agreed that the Blomberg assay relies on the measurement of NADH. The parties agree that it can be used to measure GPD1 activity, but disagree whether it can be used to measure GPD2 activity.

Lallemand attempted to test the GPD2 activity of the accused products by removing EDTA from the Blomberg assay buffer solution.<sup>8</sup> In his role as a retained expert for this case, Professor Winge directed Lallemand to make three modifications to the assay, which he believed would stabilize GPD2: (1) maintain the pH at 7.5, (2) provide magnesium, and (3) provide a reductor for GPD2's cystines. The parties disagree about the scientific validity of these modifications, and Winge acknowledged at the colloquy that there were no published scientific articles or studies supporting his modifications to the Blomberg assay to stabilize the GPD2 activity, nor did he run any regression analyses to try to confirm his opinion.

In the section titled Metabolite Analysis, the patent describes how "[s]upernatant obtained by centrifugation of culture samples was analyzed for glucose, acetic acid, succinic acid, lactic acid, glycerol and ethanol via HPLC analysis." (*Id.* at 16 (19:65-67); *see also id.* 19:67-20:19 (describing HPLC analysis with a Waters Alliance 2690 HPLC).) The parties

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<sup>8</sup> The parties agree that EDTA is often found in enzyme buffer solutions due to its general ability to stabilize enzymes.

agree that HPLC analysis can be used to measure the rate at which glycerol is produced during fermentation and that it is disclosed in the patent. At the colloquy, Winge opined that measuring the glycerol production was inappropriate because there was not a direct correlation between concentrations of GPD and glycerol. However, he also agreed that current technology did not support more accurate means for testing, like carbon tracking *in vivo*. Moreover, the experts agreed at the colloquy that so far there is no way to currently measure GPP activity or G-3-P production because the GPP enzymatic reaction (EC 3.1.3.21) converting G-3-P to glycerol happens so quickly.

#### **E. Sun Patent**

Lallemand asserts that the '998 patent was anticipated by International Publication No. WO 2009/111672, which the parties refer to as “Sun,” after the lead inventor, Jun Sun. The Sun patent discloses “a non-naturally occurring microbial organism that includes one or more gene disruptions occurring in genes encoding enzymes that couple long-chain alcohols (LCA) production to growth of the non-naturally occurring microbial organism.” (Sun Patent (dkt. #55-2) 4 (2:23-26).) Specifically, the microorganisms are designed to create LCA using “a malonyl-CoA-independent fatty acid synthesis (FAS) pathway and an acyl-reduction pathway.” (*Id.* (2:6-7); *see also id.* at 116 (114:2-5).) Sun explains that “some embodiments” contain “one or more gene disruptions in the eukaryotic organism encoding an enzyme,” such as “a glycerol-3-phosphate dehydrogenase shuttle[ or] an external NADH dehydrogenase.” (*Id.* at 61-62 (59:24-60:3).) The cells “disrupt[] . . . the glycerol-3-phosphate dehydrogenase shuttle.” (*Id.* at 63 (61:26-28); *id.* at 64 (62:13-14) (“In some embodiments, the ethanol-specific alcohol dehydrogenases is disrupted to prevent ethanol formation.”).) Further, some embodiments

detail “a non-naturally occurring eukaryotic organism [that] uses a heterologous acetaldehyde dehydrogenase (acetylating).” (*Id.* at 69 (67:15-16).) Sun specifies “exemplary bacteria” and “[e]xemplary yeasts or fungi” that can be chosen to be the “[h]ost microbial organism[,],” including *Saccharomyces cerevisiae*. (*Id.* at 32-33 (30:27-31:2).)

As defendants’ expert, Professor Winge compared the claim elements of the ’998 patent with the disclosures in Sun. His analysis can be summarized as follows:<sup>9</sup>

Label	Required Element	Sun References
[a]	Transgenic yeast cells comprising one or more recombinant heterologous, nucleic acid sequences encoding a protein with NAD <sup>+</sup> -dependent acetylating acetaldehyde dehydrogenase activity (EC 1.2.1.10)	2:23-24; 30:27-31:2; 59:24-60:11; 67:15-25
[b]	wherein said cells lack enzymatic activity needed for the NADH dependent glycerol synthesis, or said cells have a reduced enzymatic activity with respect to the NADH-dependent glycerol synthesis compared to a corresponding wild-type yeast cell, and	59:24-60:11; 61:1-62:2; 62:3-22; 65:23-27; 68:5-30
[c]	wherein said cells are free of NAD-dependent glycerol 3-phosphate dehydrogenase activity or have reduced NAD-dependent glycerol 3-phosphate dehydrogenase activity compared to corresponding wild-type cells, and/or	59:24-60:11; 61:1-62:2; 62:3-22; 65:23-27; 68:5-30
[d]	wherein the cells are either free of glycerol phosphate phosphatase activity or have reduced glycerol phosphate phosphatase activity compared to corresponding wild-type cells, and	59:24-60:11; 61:1-62:2; 62:3-22; 65:23-27; 68:5-30
[e]	which comprise a genomic mutation in at least one gene selected from the group consisting of GPD1, GPD2, GPP1 and GPP2, and	59:24-60:11; 61:1-62:2; 62:3-22; 65:23-27; 68:5-30
[f]	wherein said cells further comprise one or more nucleic acid sequences encoding an acetyl-Coenzyme A synthetase activity (EC 6.2.1.1) and	61:1-62:2; 62:3-22; 114:2-9
[g]	one or more nucleic acid sequences encoding NAD <sup>+</sup> -dependent alcohol dehydrogenase activity (EC 1.1.1.1).	61:1-62:2; 62:3-22; 114:2-9

<sup>9</sup> (*See* Pls.’ Reply to Defs.’ Resp. to Pls.’ PFOF (dkt. #92) ¶¶ 119-22, 124-27, 129-31, 133-39, 141-43, 146-57.)

[h]	The cells of claim 1 are <i>Saccharomycetaceae</i> , <i>Kluyveromyces</i> , <i>Pichia</i> , <i>Zygosaccharomyces</i> , or <i>Brettanomyces</i> .	30:27-31:2
[i]	The cells of claim 1, wherein at least one said mutation is a complete deletion of said gene in comparison to the corresponding wild-type yeast gene	59:24-60:11; 61:1-62:2; 62:3-22; 65:23-27; 68:5-30

Plaintiffs dispute that Sun discloses genetic modifications to the genes encoding GPD or GPP.<sup>10</sup> Plaintiffs also dispute whether: (1) Sun discloses a single embodiment with all the limitations of the asserted claims; and (2) Sun would have led a person of ordinary skill in the art to combine its teachings to create yeast cells for reducing the production of glycerol and increasing production of ethanol as disclosed in the '998 patent.

#### F. Accused Products

Defendants apparently offer for sale two genetically modified yeast cells, TFY+ and YP3, that are designed to reduce the production of glycerol. Both products contain nucleic acid sequences that encode an NAD<sup>+</sup>-dependent alcohol dehydrogenase activity (EC 1.1.1.1). TFY+ uses a transgenic *S. cerevisiae* to produce ethanol through the fermentation of partially or totally liquefied grains. Lallemand explains that TFY+ increases the production of ethanol by: (1) reducing glycerol production; (2) improving yeast's tolerance of industrial fermentation conditions; and (3) reducing the need for glucoamylase (an enzyme that converts starch into glucose). The parties agree that glycerol production is reduced but not entirely eliminated, and

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<sup>10</sup> Defendants characterize this dispute as follows: "DSM does not dispute that Sun discloses each and every limitation of the Asserted Claims," rather DSM disputes whether Sun discloses the combination of all the elements. (Defs.' Opp'n (dkt. #77) 27 & n.16.) At the expert colloquy, the anticipation discussion centered on an embodiment on pages 65-67 and in Figure 18 of Sun. There is no dispute that the embodiment discussed at those pages of Sun and referenced in Figure 18 does not include GPD/GPP gene modification for the purpose of reducing glycerol production in the making of ethanol.

that TFY+ also contains glycoamylase from *S. fibuligera*. Thus, the parties agree that the first and third methods of boosting ethanol production are present in the accused products, while DSM contends that Lallemand has not proven that the second method is present.

The parties also agree that the yeast cells of TFY+ lack the GPD2 gene and are modified with genes from *Bifidobacterium adolescentis*, which “provide pyruvate formate lyase activating enzyme (pflA), pyruvate formate lyase (pflB), and the bifunctional acetaldehyde-CoA/alcohol dehydrogenase AdhE.” (Defs.’ Reply to Pls.’ Resp. to Defs.’ PFOF (dkt. #95) ¶ 49.) Thus, TFY+ converts pyruvate to ethanol and oxidizes NADH to NAD+. Internal Lallemand documents refer to TFY+ as strain M8841. Plaintiffs contend that Lallemand also sells strain M10156 as TFY+ to one customer.

Derived from TFY+, YP3 contains the same modifications. It was created to overexpress Stl1, a native glycerol transport protein. The parties disagree about the purpose of this overexpression: Lallemand contends that “[t]he purpose of Stl1 in TFY+ is to attenuate Gpd1 function by increasing the intracellular concentration of glycerol,” while DSM contends that Lallemand’s R&D documents show instead that the Stl1 glycerol transport protein’s overexpression in YP3 “downregulates Gpd1 via feedback inhibition.” (*Id.* ¶ 60.) The parties agree that this modification decreases the amount of extracellular glycerol and helps the yeast remain osmotically balanced under stressful conditions. Internal Lallemand documents refer to YP3 as strain 12156.

Additionally, the parties agree that a number of Lallemand’s documents refer to “downregulat[ion],” including “of the *gpd1/gpd2* genes.” (*See* Defs.’ Resp. to Pls.’ Addl. PFOF ¶¶ 31-32; LAL00041342 (dkt. #47-48) 1; International Patent Publication No. WO 2012/138942 (dkt. #47-47) ¶ 150.) However, they disagree about what that means.

### G. Person of Ordinary Skill in the Art

Finally, in the summary judgment briefing, the parties dispute what would qualify a person to be one of ordinary skill in the art, although that dispute does not appear to be material to their motions. Regardless, at the colloquy, the parties' experts agreed that in order for one to practice the patent, they would need a master's level understanding of biochemistry, or biological or mechanical engineering. They also agree that that person would require familiarity with the use of multiple enzymes in biochemical reactions, as well as background processes, and would have experience with metabolic flux. Therefore, the court finds that this is a reasonable floor for one with sufficient skill in the art to practice the invention, and that such an individual would understand the basic elements of the claims well enough to know when to consult others with the necessary specific expertise to implement some of the actual steps for industrial scale ethanol production through the use of modified yeast cells.

## OPINION

### FINAL CLAIMS CONSTRUCTION

As explained at the time of the court's earlier, proposed constructions, "the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). For this reason, the right to exclude "begins and ends . . . with the actual words of the claim." *Renishaw PLC v. Marposs Societa' Per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998). The goal of claims construction "is to give claim terms the meaning understood by a person of ordinary skill in the art at the time of invention." *Mass. Inst. of Tech. v. Shire Pharms., Inc.*, 839 F.3d 1111, 1118

(Fed. Cir. 2016) [hereinafter *MIT*] (citing *Phillips*, 415 F.3d at 1312-14). While this includes “a heavy presumption that claim terms are to be given their ordinary and customary meaning,” *id.* at 1118 (quoting *Aventis Pharm. Inc. v. Amino Chems. Ltd.*, 715 F.3d 1363, 1373 (Fed. Cir. 2013)), this “meaning” is based on the understanding of a person of ordinary skill in the art after reading the entire patent, *id.* (quoting *Phillips*, 415 F.3d at 1321). *See also Renishaw*, 158 F.3d at 1250 (“Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim.” (citing *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 389 (1996))).

For patent claims in highly specialized fields of study, like that at issue here, “determining the ordinary and customary meaning of the claim requires examination of terms that have a particular meaning in a field of art,” yet are “not immediately apparent,” which requires the court to examine intrinsic and extrinsic evidence “concerning the relevant scientific principles, the meaning of technical terms, and the state of the art.” *Phillips*, 415 F.3d at 1314 (quoting *Innova*, 381 F.3d at 1116).<sup>11</sup> Similarly, while the “ordinary meaning” inquiry remains “an objective baseline from which to begin claim interpretation,” *id.* at 1313 (citing *Innova*, 381 F.3d at 1116), where a patent fails to explicitly define a disputed or arguably ambiguous term, the court may look to the patent as a whole, including its prosecution history, to determine that term’s meaning, *Wi-LAN USA, Inc. v. Apple Inc.*, 830 F.3d 1374, 1387 (Fed. Cir. 2016) (citing *Phillips*, 415 F.3d at 1315). *See also Renishaw*, 158 F.3d at 1248 (“The intrinsic evidence, and, in some cases, the extrinsic evidence, can shed light on the meaning of

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<sup>11</sup> Intrinsic evidence includes the patent itself and the file history, while extrinsic evidence includes evidence like expert testimony, dictionaries, inventor testimony, technical treatises and articles, or evidence of prior art. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996).

the terms recited in a claim, either by confirming the ordinary meaning of the claim terms or by providing special meaning for claim terms.” (citing *Vitronics*, 90 F.3d at 1583)). Still, claims construction is viewed as a question of law, *Wi-LAN*, 830 F.3d at 1381, reserved only for the court, *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S.Ct. 831, 835 (2015).

Here, the parties dispute the proper construction of four terms, all found in claim 1. (See Joint Statement on Claims Construction (dkt. #44) 2-3; '998 Patent (dkt. #1-1) 40 (67:12-37).)<sup>12</sup> Plaintiffs claim that all four of their proposed constructions are faithful to the terms’ “[p]lain and ordinary meaning[s],” although even they put a gloss on certain terms, while defendants claim that some terms require further construction to be consistent with the claimed invention and prosecution history. (Joint Statement on Claims Construction (dkt. #44) 2-3.) With emphasis on the terms in dispute, Claim 1 specifies:

1. Transgenic yeast cells comprising one or more recombinant heterologous, nucleic acid sequences encoding a protein with NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase activity (EC 1.2.1.10),  
wherein said cells lack enzymatic activity needed for the NADH-dependent glycerol synthesis, or  
said cells have a reduced enzymatic activity with respect to the NADH-dependent glycerol synthesis  
compared to a corresponding wild-type yeast cell, and  
wherein said cells are free of NAD-dependent glycerol 3-phosphate dehydrogenase activity or have reduced NAD-dependent glycerol 3-phosphate dehydrogenase activity compared to corresponding wild-type cells, and/or  
wherein the cells are either free of glycerol phosphate phosphatase activity or have reduced glycerol phosphate phosphatase activity compared to corresponding wild-type cells, and  
which comprise a genomic mutation in at least one gene selected from the group consisting of GPD2, GPD2, GPP1 and GPP2, and  
wherein said cells further comprise one or more nucleic acid sequences encoding an acetyl-Coenzyme A synthetase activity

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<sup>12</sup> As noted during the expert colloquy, the parties appear to disagree about the meaning of some aspects of other phrases, like “corresponding wild yeast cells” that is addressed below and, therefore, may yet require a further construction before consideration by the trier of fact at trial.

(EC 6.2.1.1) and one or more nucleic acid sequences encoding NAD<sup>+</sup>-dependent alcohol dehydrogenase activity (EC 1.1.1.1).

(’998 Patent (dkt. 1-1) 40 (67:12-37) (emphasis added).) The court addresses each of the four disputed terms below.

Term 1	
“one or more recombinant heterologous, nucleic acid sequences encoding a protein with NAD <sup>+</sup> -dependent acetylating acetaldehyde dehydrogenase activity (EC 1.2.1.10)”	
DSM’s Proposed Construction	Lallemand’s Proposed Construction
“one or more recombinant heterologous, nucleic acid sequences that encode a protein having NAD <sup>+</sup> -dependent acetylating acetaldehyde dehydrogenase activity (EC 1.2.1.10)”	“a recombinant heterologous, nucleic acid encoding an NAD <sup>+</sup> -dependent acetylating acetaldehyde dehydrogenase enzyme”

Plaintiff DSM proposes changing “nucleic acid sequences *encoding* a protein with NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase activity” to “nucleic acid sequences *that encode* a protein having NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase activity.” In contrast, defendant Lallemand proposes: (a) limiting the cells to having *a* “recombinant heterologous, nucleic acid” instead of the possibility of *one or more* “recombinant heterologous[] nucleic acid sequences” and (b) encompassing an “NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase *enzyme*” instead of “a protein with NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase *activity* (EC 1.2.1.10).”

Plaintiffs explain that EC numbers classify enzymes based on the reaction they catalyze, which means that “EC 1.2.1.10” is reserved for proteins that catalyze the conversion of acetyl-Coenzyme A to acetaldehyde. (Pls.’ Opening Br. (dkt. #59) 15.) In response, defendants argue that the claim specifies a protein that has “NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase activity” -- a particular enzymatic activity. (Defs.’ Opp’n (dkt. #77) 26-27.)

Plaintiffs characterize this dispute as a question whether AdhE and other bifunctional acetylating acetaldehyde dehydrogenase enzymes are included, adding that because the patent identifies AdhE it would be improper to exclude a preferred embodiment. (Pls.' Reply (dkt. #97) 8-9.)

The court will not adopt either side's proposed construction, having determined that the plain and ordinary meaning of this term is indeed appropriate. As an initial matter, the court sees no reason to limit the term to a single "recombinant heterologous[] nucleic acid," where the term specifies "one or more . . . sequences." As to plaintiffs' proposal to change the word "encoding" to "that encode," the court is unconvinced that there is a meaningful difference. And importantly, if there is a difference, there is no basis to depart from the claim's actual syntax.

The court also rejects defendants' proposed change of "NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase activity (EC 1.2.1.10)" to "NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase enzyme." As plaintiffs point out, the Enzyme Commission number -- the EC number -- is a unique four-digit number which describes the chemical reaction catalyzed. Specifically, the first digit identifies one of six classes; "the second and third digits describe the type of reaction catalyzed"; and "the fourth digit is employed to distinguish between enzymes of the same function on the basis of the actual substrate in the reaction catalyzed." Douglas S. Clark & Harvey W. Blanch, *Biochemical Engineering* 1 (2d. ed. 1997). The enzyme identified by "EC 1.2.1.10" is "acetaldehyde dehydrogenase (acetylating)." Information on EC 1.2.1.10 -- acetaldehyde dehydrogenase (acetylating), BRENDA, <https://www.brenda-enzymes.org/enzyme.php?ecno=1.2.1.10> (last visited Mar. 1, 2018). Replacing "activity" with "enzyme" would appear to change the claim's meaning since it is the

*activity* -- not the enzyme that performs the activity -- that is at the heart of this portion of the claim term and, indeed, the invention itself. Thus, this term simply means “one or more recombinant heterologous, nucleic acid sequences encoding a protein with NAD<sup>+</sup>-dependent acetylating acetaldehyde dehydrogenase activity (EC 1.2.1.10).” (*See* ’998 Patent (dkt. 1-1) 40 (67:12-15).)

Term 2	
“said cells . . . have reduced NAD-dependent glycerol 3-phosphate dehydrogenase activity [GPD] compared to corresponding wild-type cells”	
DSM’s Proposed Construction	Lallemand’s Proposed Construction
“the cells exhibit a reduction in the rate of the reaction catalyzed by GPD in the enzymatic production of glycerol compared to the corresponding wild-type yeast cells”	“the cells include modifications to one or more genes encoding GPD activity such that GPD is expressed considerably less than in the wild-type yeast cell or such that one or more genes encode GPD with reduced activity”

Term 3	
“said cells have a reduced enzymatic activity with respect to the NADH-dependent glycerol synthesis compared to corresponding wild-type cells”	
DSM’s Proposed Construction	Lallemand’s Proposed Construction
“the cells exhibit a reduction in the rate of enzymatic production of glycerol compared to the corresponding wild-type yeast cell”	“the cells include modifications to one or more genes encoding one or more enzymes needed for NADH-dependent glycerol synthesis such that one or more enzymes are expressed considerably less than in the wild-type yeast cell or such that one or more genes encode a polypeptide with reduced activity”

The parties discuss the second and third terms together, and the court will follow suit, while actually construing the terms in dispute individually. DSM argues that “enzymatic activity” is defined by enzymology and metabolic engineering as “the enzyme-catalyzed rate of

product conversion under a given set of conditions, usually measured as the concentration change (substrate consumption or product formation) per unit time,” which is usually expressed “in terms of units based upon the rate of the reaction that the enzyme promotes.” (Pls.’ Opening Br. (dkt. #59) 18.) According to plaintiffs, therefore, “‘enzymatic activity’ is synonymous with the rate of the enzyme-catalyzed reaction, with an increased enzymatic activity corresponding to an increased reaction rate (due to lower activation energy) and a reduced enzymatic activity corresponding to a reduced reaction rate (due to a higher activation energy).” (*Id.* at 19.) Thus, plaintiffs argue that both “reduced enzymatic activity terms” should be construed to mean: “(1) the cells exhibit a reduction in the rate of enzymatic production of glycerol compared to corresponding wild-type yeast cells; and (2) the cells exhibit a reduction in the rate of the reaction catalyzed by GPD in the enzymatic production of glycerol compared to the corresponding wild-type yeast cells.” (*Id.*)

Defendants counter that plaintiffs’ proposed constructions would render *any* reduction in glycerol production an infringement, but that unreasonably and unnecessarily simplifies the claims. Lallemand further argues that DSM’s reading must be rejected for three additional reasons: (1) inappropriately including “enzymatic production of glycerol” in both terms would make one superfluous; (2) intrinsic evidence establishes that “enzymatic activity” refers to the *amount of enzyme* expressed making it improper to equate enzymatic activity with the rate of substrate consumption or product formation; and (3) no extrinsic evidence requires a different meaning for “enzymatic activity.” (Defs.’ Opp’n (dkt. #77) 7-8.)

In reply, plaintiffs first point out that their construction does not make one term superfluous because a reduction in enzymatic activity could be achieved under Claim 1 by deleting GPP activity -- without necessarily impacting the GPD-catalyzed reaction at all. (Pls.’

Reply (dkt. #97) 12.) Secondly, plaintiffs explain that enzymatic activity cannot mean the “amount of enzyme” because enzymatic activity is dependent on other factors, such as temperature, pH, and substrate concentration. (*Id.* at 26.) Plaintiffs also argue that the structural requirement of genetic modification comes from a different term, and it need not (and should not) be read into terms 2 and 3, especially because the specification contemplates other methods. (*Id.* at 13-14; Pls.’ Opening Br. (dkt. #59) 19-20.) Third, plaintiffs argue that defendants’ proposed construction would actually exclude the embodiment introducing a separate metabolic pathway to compete with the NADH-glycerol synthesis pathway. (Pls.’ Reply (dkt. #97) 15-16.)

Finally, defendants likewise emphasize that their proposed constructions of terms 2 and 3 differ from plaintiffs’ in two ways: (1) the meaning of “enzymatic activity”; and (2) the structural requirements necessary for a “reduction.” (Defs.’ Opening Br. (dkt. #64) 15.) As to the meaning of “enzymatic activity,” Lallemand proposes construing it as a measure of the expression or availability of GPD in the cell, while DSM construes it as a measurement of the rate of the GPD-catalyzed reaction. As to the structural requirements necessary to measure “a reduction,” Lallemand proposes tying the reduction to the genetic modification, while DSM does not.

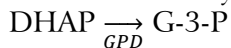
As an initial matter, “activity” is a noun that refers here to a metabolic process, whose “rate” would normally be understood by one skilled in the art to be measured by the change in moles of a substrate converted or of its converted product per unit of time. Here, GPD (an enzyme) catalyzes the conversion of dihydroxyacetone phosphate (“DHAP”) to glycerol-3-phosphate (“G-3-P”), so that “activity” is measured by the change in DHAP or the change in

G-3-P over time.<sup>13</sup> Stated another way, the rate of activity may be calculated by a rate law, often written with an equation first postulated by Michaelis and Menten<sup>14</sup> as follows:  $\frac{mol}{s} = \frac{(k_{cat})(E_0)(substrate)}{K_m + (substrate)}$ . In this rate law,  $k_{cat}$  refers to the rate constant that describes the maximum rate of enzymatic reaction -- when the enzyme is saturated with substrate (i.e., when the rate is no longer dependent on substrate concentration);  $E_0$  refers to the abundance of the enzyme; and substrate is the amount of the substance on which the enzyme acts;  $K_m$  refers to the enzyme saturation constant (i.e., the concentration of the substrate where the rate is  $\frac{1}{2}$  ( $k_{cat}$ )). The characteristic enzyme constants,  $k_{cat}$  and  $K_m$  can be changed through modification of the enzyme itself,<sup>15</sup> such that the maximum rate of reaction is altered and/or its saturation point is altered, while  $E_0$  can be altered through genetic modification or mutation, as suggested by the patent-in-suit to prevent or change the production of the enzyme.

Turning to term 2, the plain language simply provides that the patented cells have reduced GPD activity as compared to wild-type cells. Contrary to defendants' proposal, this language does not limit the reduction in the rate of activity to a genetic modification removing or reducing production of GPD; indeed, term 2 does not specify the means by which the

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<sup>13</sup> The conversion of DHAP to G-3-P generally involves a 1:1 reaction ratio so the rate of change in either the concentration of DHAP or the concentration of G-3-P divided by the amount of time should provide an approximately equal measure of activity. This reaction can be displayed as:



<sup>14</sup> See Kenneth A. Johnson & Roger S. Goody, *The Original Michaelis Constant: Translation of the 1913 Michaelis-Menten Paper*, 50 *Biochemistry* 8264 (2011), <https://pubs.acs.org/doi/abs/10.1021/bi201284u>.

<sup>15</sup> The catalytic constant may be altered by the environmental conditions of the activity, such as pH and temperature, but here those conditions are presumably held constant.

reduction in  $\frac{mol}{s}$  is achieved.<sup>16</sup> Thus, the language of this term permits a change in  $k_{cat}$ ,  $K_m$ ,  $E_0$  or substrate.

Accordingly, plaintiffs' proposal specifying that the cells "exhibit a reduction in the rate of the reaction catalyzed by GPD" is a clarification of the "have reduced NAD-dependent glycerol 3-phosphate dehydrogenase activity [GPD]" language found in the term. In its proposed claim construction, the court indicated that plaintiffs' addition of "enzymatic production of glycerol" further clarified that the claim term is talking about GPD's function in the production of glycerol. However, following the expert colloquy, the court recognizes that a more accurate clarification of the role of GPD would be to specify that NADH-dependent GPD catalyzes the reaction of DHAP to glycerol-3-phosphate. As such, the court will construe term 2, as "said cells exhibit a reduction in the rate of the reaction catalyzed by NADH-dependent GPD in the enzymatic production of glycerol 3-phosphate compared to the corresponding wild-type yeast cells."

For similar reasons, plaintiffs' proposed construction of term 3 is closer to the mark than defendants'. Term 3 specifies that the patented cells have decreased metabolic activity regarding the NADH-dependent glycerol synthesis as compared to wild-type cells. As with

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<sup>16</sup> In fact, genetic modification is required by a different term. ('998 Patent (dkt. #1-1) at 40 (67:30-32 ("which comprise a genomic mutation in at least one gene selected from the group consisting of GPD1, GPD2, GPP1, and GPP2")); *id.* (68:39-41 ("The cells of claim 1, wherein at least one said mutation is a complete deletion of said gene in comparison to the corresponding wild-type yeast gene.")).) Reading the genetic modification requirement into this term would make the later term superfluous. *See WiLAN*, 830 F.3d at 1391 (noting the "presumption that differently worded claims cover different claim scope," stemming from "the legal canon of construction against superfluity" such that "[a] construction that would cause two differently worded claims to cover exactly the same claim scope would render one of the claims superfluous, so [courts] apply a presumption against such constructions").

term 2, term 3 does not require genetic modification.<sup>17</sup> Accordingly, plaintiffs’ proposed language -- “exhibit a reduction in the rate” -- provides appropriate clarification. However, the term’s construction should maintain a specific reference to the “NADH-dependent glycerol synthesis.” Thus, term 3 will be construed to mean “said cells exhibit a reduction in the rate of NADH-dependent glycerol production compared to the corresponding wild-type yeast cell.”

<b>Term 4</b>	
“wherein said cells further comprise one or more nucleic acid sequences encoding an acetyl-Coenzyme A synthetase activity (EC 6.2.1.1) and one or more nucleic acid sequences encoding NAD+-dependent alcohol dehydrogenase activity (EC 1.1.1.1)”	
<b>DSM’s Proposed Construction</b>	<b>Lallemand’s Proposed Construction</b>
“the cells comprise (i) one or more nucleic acid sequences that encode an acetyl-Coenzyme A synthetase activity and (ii) one or more nucleic acid sequences that encode an NAD+-dependent dehydrogenase activity”	“wherein said cells further comprise one or more nucleic acid sequences encoding an acetyl-Coenzyme A synthetase activity and one or more nucleic acid sequences encoding NAD+-dependent alcohol dehydrogenase activity, whereby the cells are net consumers of acetate/acetic acid such that the cells can reoxidize NADH by the reduction of acetate/acetic acid to ethanol via NADH-dependent reactions in place of glycerol synthesis and whereby the cells grow preferentially in the presence of acetate”

The parties basically agree on the substance of DSM’s proposed construction.<sup>18</sup> The dispute arises from Lallemand’s three additional limitations: (1) “the cells are net consumers of acetate/acetic acid”; (2) “the cells can reoxidize NADH by the reduction of acetate/acetic

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<sup>17</sup> See *supra*, note 16.

<sup>18</sup> There are two slight differences: (1) plaintiffs modify “encoding” to “that encode,” while defendants use “encoding” as found in the disputed term; and (2) plaintiffs remove the “alcohol” from the “NAD+-dependent alcohol dehydrogenase activity,” while defendants keep it in, consistent with the disputed term. (The addition of the romanettes in plaintiffs’ proposal is non-substantive and improves readability.)

acid to ethanol via NADH-dependent reactions in place of glycerol synthesis”; and (3) “the cells grow preferentially in the presence of acetate.” Defendants argue that their additions are based on the patent applicants’ statements to distinguish the invention from the prior art. (Defs.’ Opp’n (dkt. #77) 18.) Specifically, defendants base the first addition on the patent applicants’ statement that “[t]here is no suggestion to modify a yeast cell in order to make it a net consumer of acetate”; the second addition is based on a statement that the invention “is capable of using acetate as an electron acceptor to reoxidize NADH and therefore avoids or reduces the need for glycerol synthesis”; and the third addition is based on a statement that “[t]he invention provides a yeast cell that actually grows preferentially in the presence of acetate.” (*Id.* at 24.)

Plaintiffs argue that defendants have failed to meet the “high standard” of establishing prosecution disclaimer. (Pls.’ Opening Br. (dkt. #59) 24-25 (citing *MIT*, 839 F.3d at 1119).) As to the first two additions, in particular, plaintiffs argue that the ability of the cells to use the acetate in the production of ethanol instead of glycerol is a “further advantage,” not a disclaimer. (*Id.* at 25-26.) Further, DSM argues that “Lallemand’s argument is scientifically flawed” because the proposed “functional acetate limitations are not even commensurate in scope with the functions of the nucleic acid sequences specifically recited in the disputed claim term.” (Pls.’ Reply (dkt. #97) 25-26.)<sup>19</sup> As to the remaining addition, plaintiffs argue that the patentees noted that the patented cell grew preferentially with acetate, but that that statement was not a limitation required by the claims; rather it was prompted by a Lallemand corporate

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<sup>19</sup> Specifically, DSM argues that a yeast cell with only (EC 6.2.1.1) and alcohol dehydrogenase activity (EC 1.1.1.1) (as specified in the term itself) cannot convert acetate to ethanol and that the claimed cell’s ability to “consume acetate and create ethanol stems from the acetyl-Coenzyme A synthetase and alcohol dehydrogenase activities *in combination with* the claimed acetylating acetaldehyde dehydrogenase activity.” (Pls.’ Reply (dkt. #97) 25.)

representative's admission that the accused products consume acetate. (Pls.' Opening Br. (dkt. #59) 26-27.) Plaintiffs also argue that defendants' construction defines the claimed cells "in terms of how they might be used," even though the claims do not contain that requirement. (Pls.' Reply (dkt. #97) 26.)

A patent's prosecution history sheds light on how the inventor and the Patent and Trademark Office conceptualized the patent. *Phillips*, 415 F.3d at 1317. Prosecution disclaimer is a doctrine that prevents "patentees from recapturing through claim interpretation specific meanings disclaimed during prosecution." *MIT*, 839 F.3d at 1119 (quoting *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003)). However, the doctrine only applies where the patentees' disavowal is "both clear and unmistakable." *Id.* (quoting *3M Innovative Props. Co. v. Tredegar Corp.*, 725 F.3d 1315, 1325 (Fed. Cir. 2013)). Anything short of "clear and unmistakable," which must be proved by the party attempting to invoke prosecution disclaimer, does not warrant application of the doctrine. *Id.*

Having reviewed the prosecution history, the court concludes that defendants have not met this "high standard." *See id.* at 1120. In short, did the patentees stress that acetate was beneficial? Yes. Did they say that it was critical for the invention? No. The invention teaches away from prior art by making use of a formerly disfavored metabolite. Specifically, the patentees argued that one of ordinary skill in the art would not realize the benefits of production or presence of acetate since Sonderegger was trying to *reduce* acetate production and the common understanding at the time of the invention was that the presence of acetate would be a detriment. Valadi, on the other hand, determined that "glycerol formation could be reduced even further" by altering the genes encoding GPD2, but recognized that precisely "[h]ow the redox balance in the *gpd2Δ* mutant is accomplished is not known." (*See* H. Valadi

*et al.*, *Improved Ethanol Production by Glycerol-3-phosphate dehydrogenase mutants of Saccharomyces cerevisiae*, 50 *Applied Microbiology Biotechnology* 434, 438 (1998) (dkt. #47-4) 5.) In hindsight, perhaps, someone with exceptional skill in the art would have realized that combining Sonderegger and Valadi would make the presence of acetate beneficial, but that does not make the invention obvious.

Further, these additions are not scientifically necessary. Claim 1 provides for a yeast cell that has three modifications: (1) a genetic modification to reduce the production of GPD and/or GPP; (2) the addition of alcohol dehydrogenase (EC 1.1.1.1) and acetyl-Coenzyme A synthetase (EC 6.2.1.1); and (3) the addition of acetylating acetaldehyde dehydrogenase activity (EC 1.2.1.10). Without the second modification, the yeast cells would not be able to function adequately because the only modification would have been to delete GPD or GPP, meaning that the cells would not be able to use glycerol production to achieve redox balance, thereby stymying the production of ethanol. In the invention, acetate is catalyzed to become acetyl-CoA, which in turn permits the acetylating acetaldehyde dehydrogenase activity to produce ethanol, via alcohol dehydrogenase. Thus, term 4 provides the clarification of acetate as the basis for the redox reaction, making defendants' additional limitations unnecessary. At minimum, defendants have not proven the patentees' disavowal clearly and unmistakably.

Thus, the court construes this term to mean "the cells comprise (i) one or more nucleic acid sequences encoding an acetyl-Coenzyme A synthetase activity (EC 6.2.1.1) and (ii) one or more nucleic acid sequences encoding an NAD<sup>+</sup>-dependent alcohol dehydrogenase activity (EC 1.1.1.1)."

## SUMMARY JUDGMENT

Summary judgment is appropriate where there are “no genuine dispute[s] as to any material fact[s] and the movant is entitled to judgment as a matter of law.” Fed. R. Civ. P. 56(a). The moving party bears the burden of showing that the facts material to the motion are not in dispute. *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986); *see also Conroy v. Reebok Internat’l, Ltd.*, 14 F.3d 1570, 1575 (Fed. Cir. 1994) (“The moving party, however, need not produce evidence showing the absence of a genuine issue of material fact but rather may discharge its burden by showing the district court that there is an absence of evidence to support the nonmoving party’s case.” (internal citations omitted)).

Where it has the burden of proof, the nonmoving party may not avoid summary judgment merely by showing that some facts are in dispute; rather, it must establish that one or more factual disputes might affect the ultimate outcome of the suit under governing law. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247-48 (1986). Although the court must “take all facts and reasonable inferences in the light most favorable to” the nonmoving party, *Helman v. Duhaime*, 742 F.3d 760, 761 (7th Cir. 2014), the nonmoving party with the burden of proof must still come forward with enough evidence to support a reasonable jury verdict in its favor, *Delta Consulting Grp., Inc. v. R. Randle Constr., Inc.*, 554 F.3d 1133, 1137 (7th Cir. 2009). Summary judgment is “not a dress rehearsal or practice run,” but the “put up or shut up moment” in which a proponent of facts must show what evidence it has to convince a trier of fact to accept its version of events. *Nichols v. Nat’l Union Fire Ins. Co. of Pittsburgh, PA*, 509 F. Supp. 2d 752, 760 (W.D. Wis. 2007) (quoting *Schacht v. Wis. Dep’t of Corr.*, 175 F.3d 497, 504 (7th Cir. 1999)).

Here, plaintiffs seek summary judgment on defendants’ anticipation defense (Pls.’ Mot.

Judicial Construction & Partial Summ. J. (dkt. #58) 3), and Defendants seek summary judgment of invalidity on the basis of indefiniteness and no willful infringement. (Defs.’ Mot. Summ. J. (dkt. #61) 1.)<sup>20</sup>

## I. Anticipation

Because it is the strongest, the court will begin with plaintiffs’ motion for summary judgment on defendants’ anticipation defense. Evaluating a claim of anticipation involves a two-step inquiry. The first step requires proper construction of the meaning and scope of the claims. *Power Mosfet Techs., L.L.C. v. Siemens AG*, 378 F.3d 1396, 1406 (Fed. Cir. 2004). “The second step in the analysis requires a comparison of the properly construed term to the prior art[.]” *Id.* To demonstrate anticipation, “the proponent must show ‘that the four corners of a single, prior art document describe every element of the claimed invention.’” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Xerox Corp. v. 3Com Corp.*, 458 F.3d 1310, 1322 (Fed. Cir. 2006)). Importantly, “[b]ecause the hallmark of anticipation is prior invention, the prior art reference . . . must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements ‘arranged as in the claim.’” *Id.* (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). This means that the prior art must detail all the limitations “arranged or combined in the same way as in the claim.” *Id.* at 1370. Thus, “it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to

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<sup>20</sup> DSM did not affirmatively move for summary judgment of infringement, but requests it in its opposition. (Pls.’ Opp’n (dkt. #74) 36.)

achieve the claimed invention.” *Id.* at 1371.<sup>21</sup>

As defendants emphasize, “[h]owever, a reference can anticipate a claim even if it d[oes] not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would at once envisage the claimed arrangement or combination.” *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1341 (Fed. Cir. 2016) (first alteration added) (internal citations and quotation marks omitted); *id.* at 1344 (“[A] reference may still anticipate if that reference teaches that the disclosed components or functionalities may be combined and one of skill in the art would be able to implement the combination.” (internal citations omitted)); *see also Purdue Pharma*, 811 F.3d at 1351 (“A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference.” (internal citation omitted)). Although anticipation is ultimately a question of fact, “it may be decided on summary judgment if the record reveals no genuine dispute of material fact.” *Leggett & Platt, Inc. v. VUTEk, Inc.*, 537 F.3d 1349, 1352 (Fed. Cir. 2008) (quoting *Golden Bridge Tech., Inc. v. Nokia, Inc.*, 527 F.3d 1318, 1321 (Fed. Cir. 2008)). Specifically, summary judgment on anticipation is appropriate if no reasonable jury could find that the patent was anticipated. *See Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1327 (Fed. Cir. 2001) (explaining summary judgment of

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<sup>21</sup> DSM relies on *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972), for the proposition that in order for a prior art reference to anticipate an invention, it “must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference” -- that all elements must be contained within a single embodiment. However, *Arkley* was not intended by the Court of Customs and Patent Appeals to alter the test for anticipation. *See In re Schaumann*, 572 F.2d 312, 317 (C.C.P.A. 1978) (*Arkley* “should not be interpreted as establishing a new test for determining whether an invention has been described in a reference within the meaning of 35 U.S.C. s 102.”). *Arkley* instead requires the disclosures in the prior art be “directly related” to prevent “impermissible picking and choosing.” *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1358-59 (Fed. Cir. 2016) (citing *Arkley*, 455 F.2d at 587).

anticipation for the defendant “is proper if no reasonable jury could find that the patent is not anticipated”). “Evidence of invalidity must be clear as well as convincing.” *Schumer v. Laboratory Computer Sys., Inc.*, 308 F.3d 1304, 1315 (Fed. Cir. 2002). As such, “[t]ypically, testimony concerning anticipation must be testimony from one skilled in the art and must identify each claim element, state the witnesses’ interpretation of the claim element, and explain in detail how each claim element is disclosed in the prior art reference.” *Id.* Conclusory statements by experts -- or attorneys -- are insufficient. *See id.* at 1315-16.

Defendants assert that International Patent Publication No. WO 2009/111672 (“Sun”) anticipated the invention. (*See* Pls.’ Mot. Judicial Construction & Partial Summ. J. (dkt. #58) 3.) At summary judgment, plaintiffs begin by arguing that the microorganisms described in Sun are distinguishable from those of the present invention, which is certainly true as a matter of fact. Sun organisms create long chain alcohols, to the detriment of ethanol production, and rely on the “the incorporation of a malonyl-CoA-independent fatty acid synthesis pathway and an acyl-reduction pathway.” (Pls.’ Opening Br. (dkt. #59) 29.) Plaintiffs argue that defendants fail to provide enough evidence showing that Sun disclosed the invention, choosing instead to improperly “pick[] and choose[] beneficial excerpts from Sun in order to stitch together various elements of the Asserted Claims.” (*Id.*) In particular, plaintiffs accuse defense expert, Professor Winge, of “improperly treat[ing] the Asserted Claims ‘as mere catalogs of separate parts, in disregard to the part-to-part relationships set forth in the claims and that give the claims their meaning,’” while failing to identify a single embodiment containing all necessary claim elements, such that there is no clear and convincing evidence of anticipation. (*Id.* at 31-32 (quoting *Therasence, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010)).)

Plaintiffs also argue that: (1) “Sun does not disclose each element arranged into a

transgenic yeast cell as in the Asserted Claims” because “the only embodiments of Sun purportedly meeting elements [f] and [g] of the Asserted Claims are missing other required elements”; (2) defendants fail to “identify any disclosure in Sun that would have led a person of ordinary skill in the art to combine its various teachings to achieve the Asserted Claims”; (3) defendants fail to “explain why a person of ordinary skill in the art would have selected particular teachings from the various embodiments of Sun and combined them to achieve the Asserted Claims”; and (4) Sun “does not disclose any transgenic yeast cells having all of the elements arranged in the Asserted Claims.” (*Id.* at 35-36.) As to the last, plaintiffs point out that Sun fails to disclose a preferred example with a genetic modification to GPD or GPP genes, much less for the purpose of eliminating or reducing glycerol production in the biological manufacture of ethanol. (*Id.* at 36.)

In response, defendants argue that plaintiffs’ attempt to distinguish between the microorganisms disclosed in Sun and those disclosed in the ’998 patent is “unavailing” because the cells disclosed in the ’998 patent “can include additional structures and functions beyond those listed”; more specifically, Claim 1 is a “comprising” term, making the different use of Sun organisms “irrelevant.” (Defs.’ Opp’n (dkt. #77) 30-31.) The bulk of defendants’ opposition to plaintiffs’ motion, however, is based on the argument that a single embodiment in Sun, found on pages 65–67 and shown in figure 18, discloses all necessary claims limitations. (*See*

*id.* at 31-39.)<sup>22</sup>

In reply, plaintiffs point out that defendants' expert, Professor Winge, does *not* rely on that embodiment. Thus, defendants are left with nothing more than attorney argument, despite specialized, scientific expertise being necessary to establish anticipation by clear and convincing evidence. (*See* Pls.' Reply (dkt. #97) at 34-35.)<sup>23</sup> Additionally plaintiffs argue that: (1) Figure 18 fails to "disclose any disruption to the glycerol-3-phosphate shuttle"; (2) "there is no evidence that Sun would have led a person of ordinary skill in the art to modify Figure 18 to include" that disruption; (3) anticipation cannot be established based on a person of ordinary skill's ability to "modify Figure 18 to include a disruption to the glycerol-3-phosphate dehydrogenase shuttle"; and (4) defendants have presented no evidence showing that Sun would have directed a person skilled in the art "to combine acetylating acetaldehyde dehydrogenase activity with a disruption to the *gpd1* and/or *gpd2* genes other than Dr. Winge's conclusory expert report." (*Id.* at 35-38.) The court agrees.

To begin, while the embodiment on pages 65-67 and shown in Figure 18 *was* arguably relied on by Winge, it is discussed in the most oblique, superficial manner imaginable. (*See*

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<sup>22</sup> Defendants note that "[o]ther embodiments of Sun also arguably disclose each of the limitations of the Asserted Claims" but that "in the interest of brevity these other embodiments will not be addressed" because the embodiment on pages 65-67 "is sufficient." (Defs.' Opp'n (dkt. #77) 31 n.19.) Defendants purport to "reserve the right to use any and all other anticipating embodiments of Sun at trial, however, should the need arise." (*Id.*) This being the "put up or shut up" time for such arguments, the court simply disagrees, although defendants could move for reconsideration if they truly believe that some other embodiment addresses the court's concerns and they have a good excuse for not advancing that embodiment on summary judgment.

<sup>23</sup> Plaintiffs also argue that defendants failed to disclose this anticipation theory before summary judgment, depriving plaintiffs of an opportunity to obtain and present expert opinion in reply. (Pls.' Reply (dkt. #97) 35.) On this point, the court is less sympathetic, particularly given the expanded deadlines to disclose expert opinions and the subsequently adjusted expert schedule accommodating the ill-health of plaintiffs' original liability expert.

Pls.’ Opening Br. (dkt. #59) 33 (reflecting Winge’s reliance on Sun disclosures at 65:23-27 and 67:15-25); Sun Patent (dkt. #55-2) 69 (67:18) (stating that “such embodiments” are “shown in Figure 18”).) Even if this is enough for defendants to rely on Figure 18 to assert disclosure of all the asserted claim *elements*, it is *not* enough to save defendants’ anticipation defense because: (1) the elements are not arranged in the same way as in the ’998 patent; and (2) there is no evidence that a person of ordinary skill in the art would assemble the elements scattered about Sun into the invention claimed in the ’998 patent, particularly in light of no expert opinion that one skilled in the art would have done so based on Sun alone.

Sun is a remarkably broad patent, generally directed towards the production of dodecanol, and the embodiment relied on by defendants is buried almost sixty pages into the “Detailed Description of the Invention.”<sup>24</sup> At least arguably, this “disclosure” generally suggests “gene[] disruptions includ[ing] those encoding” YDL022W (GPD1) and YOL059W (GPD2), among numerous other enzymes (*see* Sun Patent (dkt. #55-2) 67 (65:23-26)), and the addition of acylating acetaldehyde dehydrogenase (*id.* 149 (Figure 18)) for redox, but these elements are certainly not arranged as in the ’998 patent. To the contrary, the acylating acetaldehyde dehydrogenase in Sun is introduced into the mitochondrion for production of dodecanol, instead of aiding redox for ethanol production in the cytosol. (*Id.*; *see also id.* at 8 (6:16-17) (“Figure 18 shows the formation of dodecanol in the mitochondrion by adding the mitochondrial acylating acetaldehyde dehydrogenase.”).)

Even if a reasonable jury could conclude that one skilled in the art would realize that acylating acetaldehyde dehydrogenase could be added to the cytosol instead, there is also no

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<sup>24</sup> This assumes that Sun truly discloses a single embodiment at pages 65-67 and Figure 18, which itself is uncertain.

reference to glycerol reduction. Finally, nothing suggests combining the acylating acetaldehyde dehydrogenase and the genetic disruptions for the purpose of more efficient production of ethanol. (*See id.* at 149 (Figure 18).) Thus, the elements are not arranged in the same fashion as in the '998 patent.

Tellingly, defendants' expert, Professor Winge, does not offer a valid opinion on anticipation. Instead, he expressly operated on the erroneous assumption "that a claim is invalid as anticipated if each and every limitation as set forth in the claim is described, expressly or inherently, in a single prior art reference." (Winge Invalidity Rpt. (dkt. #52) ¶ 42.) As discussed above, it is not enough that the prior art discloses all the elements, it must disclose them as arranged or combined in the claim, *Net MoneyIN*, 545 F.3d at 1369-70, or one skilled in the art must immediately derive the claim from reading the prior reference. *Blue Calypso*, 815 F.3d. at 1341. Winge opines that all the claimed elements are present in Sun, but not that one skilled in the art would read this embodiment and "at once envisage" the '998 patent, nor do defendants offer any other evidence that would permit a reasonable lay jury to so find. *Id.*; *see also In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness"); *Carrier Corp. v. Goodman Global, Inc.*, 64 F. Supp. 3d 602, 616 (D. Del. 2014) (finding attorney argument insufficient "to meet the burden of persuasion on invalidity at the summary judgment motion stage" for a patent that "involves complex technology"). Therefore, plaintiffs are entitled to summary judgment on this defense.

## II. Indefiniteness

Defendants' motion for summary judgment based on indefiniteness is a substantially closer call. "[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S.Ct. 2120, 2124 (2014). While "[s]ome modicum of uncertainty" is expected, "a patent must be precise enough to afford clear notice of what is claimed, thereby 'apprais[ing] the public of what is still open to them.'" *Id.* at 2128-29 (citations omitted). "Claim language employing terms of degree" or relative terms is not indefinite "where it provide[s] enough certainty to one of skill in the art when read in the context of the invention." *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (internal citations omitted); *One-E-Way, Inc. v. Internat'l Trade Comm'n*, 859 F.3d 1059, 1063 (Fed. Cir. 2017) (citing *Interval Licensing*, 766 F.3d at 1370); *see also id.* at 1067 ("While we note that 'virtually' is a term of degree, one that slightly expands the scope of the term 'free from interference,' the inclusion of 'virtually' in these claims does not render them indefinite."). This requires that the baseline, against which the comparison is made, be clear to those skilled in the art. *Liberty Ammunition, Inc. v. United States*, 835 F.3d 1388, 1395 (Fed. Cir. 2016). On the other hand, because a patent is presumed valid, defendants must prove invalidity by clear and convincing evidence. *See Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011); *see also* 35 U.S.C. § 282(a)-(b).

Sketching the invention's scope is particularly important "where different approaches to measurement are involved," such that "[t]he claims, when read in light of the specification and the prosecution history, must provide objective boundaries for those of skill in the art." *Dow Chem. Co. v. Nova Chems. Corp. (Canada)*, 803 F.3d 620, 630-31 (Fed. Cir. 2015) (quoting

*Interval Licensing*, 766 F.3d at 1371). This means that “the patent and prosecution history must disclose a single known approach or establish that, where multiple known approaches exist, a person having ordinary skill in the art would know which approach to select.” *Id.* at 630. Accordingly, a patent is indefinite when: (1) there are multiple ways of measuring a characteristic; (2) the method selected “could affect whether or not a given product infringes the claims”; and (3) the patent fails to inform a person of ordinary skill in the art of the appropriate measure. *Id.* at 634; *see id.* at 635 (“[A] claim term is indefinite if it leave[s] the skilled artisan to consult the unpredictable vagaries of any one person’s opinion.” (citations and quotation marks omitted)); *see also Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015) (finding claim indefinite for failing to “convey with reasonable certainty the measure of molecular weight to be used” where there were three possible ways to measure, each calculated differently and resulting in a different measurement; “the claim on its face offer[ed] no guidance on which measure of ‘molecular weight’ the claims cover[ed]”). Put another way, a claim lacking “a sufficient objective boundary around [its term of degree]” is indefinite. *Liberty Ammunition*, 835 F.3d at 1397. Like other forms of invalidity, indefiniteness must be proven by clear and convincing evidence. *One-E-Way*, 859 F.3d at 1062.

Defendants argue that they are entitled to summary judgment because the claims are indefinite. Specifically, defendants argue that to determine the scope of the term requiring “reduced NAD-dependent glycerol 3-phosphate dehydrogenase activity [GPD] compared to corresponding wild-type cells,” GPD activity must be measured, with the measurement being one of degree. (Defs.’ Opening Br. (dkt. #64) 26.) Defendants further posit that the patent only discloses one method of measuring GPD activity: the so-called Blomberg assay. (*Id.* at

27.)<sup>25</sup> If correct, and the Blomberg assay is unable to measure GPD activity -- as asserted by plaintiffs<sup>26</sup> -- then the claim “must be indefinite for failing to provide any guidance on how to determine the scope of the claim.” (*Id.*)

In particular, defendants argue that “a person of ordinary skill in the art would not be able to determine from the intrinsic evidence how to measure GPD activity” and would be left to their own devices to select the measuring method of their choice to determine if a yeast cell has reduced GPD activity compared to wild-type cells. (*Id.* at 28.) Defendants also challenge the relevance of Professor Stephanopoulos’s general opinion that “[b]ased on fundamental principles of enzyme kinetics and metabolic engineering, a yeast cell that has been engineered to eliminate expression of Gpd2 and that also reported exhibits a 30% reduction in glycerol synthesis -- like the Accused products -- necessarily has reduced Gpd activity compared to the corresponding wild-type strain.” (*Id.* at 28-29.)

To unpack these arguments, the court will begin with the Blomberg assay, which has been the source of much confusion, and arguably obfuscation, from both sides in this lawsuit. In fairness to defendants, the ’998 patent *expressly* discloses no preferred means for measuring the claimed reduction of GPD or GPP enzymatic activity, unless it is by use of the Blomberg assay. The defendants’ problem is that the patent does not support its use for purposes of

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<sup>25</sup> As is discussed in detail later in this section of the opinion, the patent states that “Glycerol-3-phosphate dehydrogenase activities were assayed in cell extracts at 30° C. as described previously (Blomberg and Adler (1989), J. Bacteriol. 171:1087-1092[]). Reaction rates were proportional to the amounts of cell extract added.” (’998 Patent (dkt. 1-1) 16 (20:37-40).)

<sup>26</sup> To be more precise, plaintiffs contend that the Blomberg assay is unable to measure GPD2 activity accurately, not GPD1 activity. (*See* Pls.’ Opp’n (dkt. #74) 42 (“The Blomberg assay . . . is suitable for measuring the relative production in Gpd1 activity in Examples 1 and 2 of the ’998 patent, both of which contain a deletion of the *gpd1* gene. However, abundant scientific evidence demonstrates that the Blomberg assay is not suitable for measuring Gpd2 activity because this enzyme is not stable in the buffer solutions used for the assay.” (internal citation omitted)).)

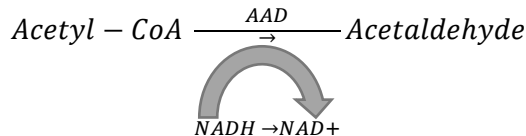
determining whether there has been a reduction in “GPD activity compared to a corresponding wild yeast cell.” Instead, the ’998 patent refers to the special use of Blomberg assays to detect cell activity *in vitro* under the heading of “Enzyme Activity Assays” in a single paragraph in Column 20, lines 20 to 45, which explains that:

Cell extracts for activity assays of NAD<sup>+</sup>-dependent acetaldehyde dehydrogenase (acetylating) were prepared from exponentially growing anaerobic batch cultures as described previously (Abbott et al., Appl. Environ. Microbiol. 75:2320-2325). NAD<sup>+</sup>-dependent acetaldehyde dehydrogenase (acetylating) activity was measured at 30° C. by monitoring the oxidation of NADH at 340 nm. The reaction mixture (total volume 1 ml) contained 50 mM potassium phosphate buffer (pH 7.5), 15 mM NADH and cell extract. The reaction was started by addition of 0.5 mM acetyl-Coenzyme A. For glycerol 3-phosphate dehydrogenase (EC 1.1.1.8) activity determination, cell extracts were prepared as described above except that the phosphate buffer was replaced by triethanolamine buffer (10 mM, pH 5) (5.19). Glycerol-3-phosphate dehydrogenase activities were assayed in cell extracts at 30° C. as described previously (Blomberg and Adler (1989), J. Bacteriol. 171:1087-1092. Reaction rates were proportional to the amounts of cell extract added. Protein concentrations were determined by the Lowry method (Lowry et al (1951) J. Biol. Chem. 193:265-275) using bovine serum albumin as a standard.

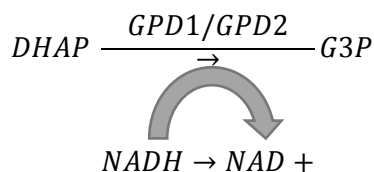
(’998 Patent (dkt. #1-1) 16 (20:21-44).)

The experts agree that this column refers to a specific experiment conducted by the patent’s inventors in which yeast cell extracts were prepared from batch cultures under conditions specified from the Abbott assay of NAD<sup>+</sup>-dependent acetaldehyde dehydrogenase (acetylating), in other words, the reaction using the AAD enzyme. (EC 1.2.1.10), which can

be depicted as:

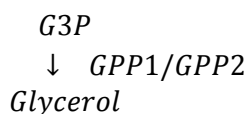


The paragraph goes on to explain that “[f]or glycerol 3-phosphate dehydrogenase (E.C. 1.1.1.8) activity determination,” cell extracts were also prepared. This reaction can be depicted as:



However, the use of either assay to measure the rate of enzymatic activity is highly doubtful, nor is its use for that purpose taught by the '998 patent.

Indeed, the parties’ experts agree that these assays were prepared for a batch culture of yeast cells that were genetically modified to express no GPD1 *and* GPD2, the essential enzymes for the production of glycerol-3-phosphate, which in the presence of GPP1 or GPP2 is rapidly converted to glycerol through E.C. 3.1.3.21.

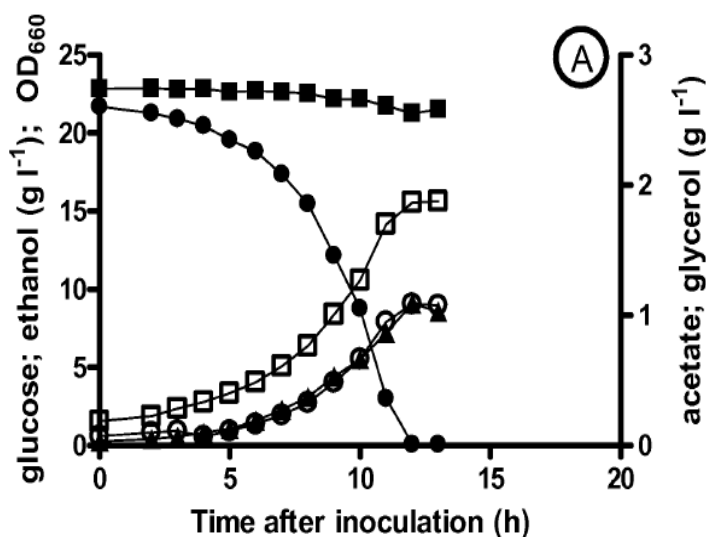


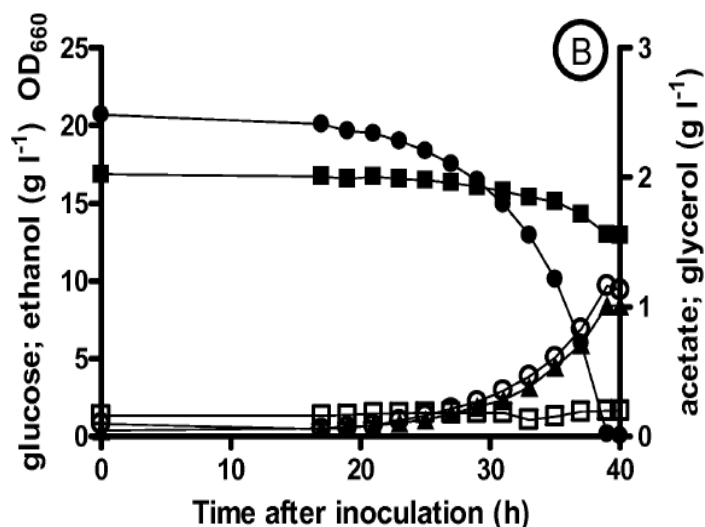
In fact, as reflected in the paragraph quoted above, the only *stated* information gleaned from opening up and assaying the cells *in vitro* was to confirm that “Reaction rates were proportional to the amounts of cell extract added,” likely referring both to the conversion of NADH to NAD<sup>+</sup> in the EC 1.1.1.8 enzymatic reaction detected in the Blomberg assay and the conversion of NADH to NAD<sup>+</sup> in the EC 1.2.1.10 enzymatic reaction found in the Abbot assay, which is what the inventors sought to confirm and basic science predicts. While measuring proportionality, what neither method of assaying cell extracts measured was changes of *rates* of

enzymatic activity over time.

This is confirmed by the first two entries on Table 3 found in Col. 21 of the '998 patent, which purport to show the presence of glycerol-3-phosphate dehydrogenase and acetaldehyde dehydrogenase as determined by the presence of NADH in the Blomberg and Abbot assays of the engineered yeast strain (IMZ132), in which no GPD1 or GPD2 was expressed as compared to corresponding wild yeast strain (IME076) at a specific point in time. Similarly, Table 3 reflects amounts of biomass produced at a specific point in time for glycerol and ethanol from substrates of glucose and acetate. To obtain the *rate* of the GPD activity in contrast, you have to look to the output on these same substrates in *in vivo* batches as plotted over time on Figures 2A and B as described in Col. 3, lines 35-49 of the '998 patent. These figures are reproduced below:

Fig. 2





That the Bloomberg assay was not used to determine the rate of GPD enzymatic activity in the patent-in-suit is hardly surprising. In fact, the only attempted use of the Bloomberg assays for this purpose in the record was by Lallemand, in 2011 and 2016, first to prove that its product had reduced GPD activity, then in an attempt to prove that it did not. In 2011, Lallemand’s use of the Bloomberg assay purported to show that the cell extracts of a yeast strain equivalent to TFY+ reduced GPD activity compared to the wild-type yeast cells, although defendants now note that some results “were within the error margin of the data.” (Defs.’ Resp. to Pls.’ Add’l PFOF (dkt. #96) ¶ 34; *see also* LAL00196466 (dkt. #47-88); LAL00196467 (dkt. #47-89).) In June 2016, Lallemand’s testing using the Bloomberg assay again purportedly showed that TFY+ had reduced GPD activity compared to the wild type cells, which defendants now explain was the result of “testing . . . performed at high protein concentration[] levels, which can lead to GPD inactivation.” (Defs.’ Resp. to Pls.’ Add’l PFOF (dkt. #96) ¶ 34; *see also* LAL00196486 (dkt. #47-99); LAL00196487 (dkt. #47-100).) Finally, at Professor Winge’s direction, Lallemand performed additional GPD activity assays, which now purport to show that the accused products had greater GPD activity than the corresponding

wild-type yeast cells, although plaintiffs' expert, Professor Stephanopoulos, found this testing to be "scientifically invalid." (See Defs.' Reply to Pls.' Resp. to Defs.' PFOF (dkt. #95) ¶¶ 92-93.)

As defendants' own use of the Blomberg assay demonstrates and plaintiffs persuasively argue, Professor Stephanopoulos has a point, particularly for use on the accused products, which deleted only GPD2, an enzyme so unstable in the buffer solution that a Blomberg assay is unlikely to reliably measure its activity. While Winge purports to correct for this instability, by among other things removing EDTA from the buffer solution, there is no recognized authority or peer reviewed study that supports this creative change in the Blomberg assay, nor does he or defendants effectively dispute plaintiffs' contention that this compound "(1) is commonly used in buffers due to its ability to stabilize enzymes, and (2) was present in all the assay buffers described in the scientific literature." (Pls.' Opening Br. (dkt. #59) 39-40.)

This then leaves one of ordinary skill in the art, and the trier of fact in this case, with the only recognized measure of GPD activity (EC 1.1.1.8), which all the experts agree is the rate of glycerol production (or the rate of reduction in the DHAP substrate), and the patent certainly does not teach that the Blomberg assay would be preferable. Regardless, the difficulties and limitations of using the Blomberg assay as a substitute for this traditional measurement of GPD activity, especially with respect to knocking out or reducing the amount of GPD2 in an anaerobic batch of yeast cells for the production of ethanol, would be so apparent that its use for that purpose is not credible, except perhaps by one searching for a way to prove the commercial viability of this practice or to prove non-infringement. Moreover, the *only* known method for measuring a change of GPP activity in the second chemical reaction (of G-3-P to glycerol (E.C. 3.1.3.21)) is to plot the rate of glycerol production. As a result, the

patent not only offers no assay for measurement of GPP enzymatic activity, but all experts agreed the reaction converting G-3-P to glycerol is nearly instantaneous, making any assay measurement of that reaction unlikely if not impossible.

This is not to suggest that measuring GPD or GPP enzymatic activity by the rate of glycerol production is ideal. The experts seem to agree that the best measure of that activity would likely be some kind of carbon-based tracking *in vivo*, but acknowledge that no such test has even been developed, much less tested to the point of consensus among experts in the field of biochemistry and, therefore, known to one of ordinary skill in the art. In short, the only recognized measurement of NAD-dependent GPD activity disclosed in the '998 patent as commonly understood by one of ordinary skill in the art is the rate of glycerol production.

In their reply brief and again during the expert colloquy, defendants nevertheless argue that “[a]t no point does the '998 patent describe measuring glycerol synthesis as a way to measure GPD activity,” and the HPLC analysis referenced by plaintiffs is found in the “Metabolite Analysis” section preceding the “Enzyme Activity Assays” section disclosing the Blomberg assay. (Defs.’ Reply (dkt. #94) 23.) Additionally, defendants note that “[g]lycerol is not the product of the reaction catalyzed by GPD; Glycerol-3-Phosphate is.” (*Id.* at 24.) But for reasons already discussed, this is mainly sophistry. Given that measurement of the rate of glycerol production is the *only* accepted scientific method for measuring GPD *and* GPP activity, much less the only one known to someone of ordinary skill in the art of industrial-scale yeast production of ethanol, the court is compelled to find that this is the proper method to measure GPD or GPP activity, even if not quite the “gold standard” that plaintiffs’ expert would make it out to be.

Having construed the proper measurement for GPD and GPP activity in claim 1, the

court turns to the defendants' last remaining challenge under the Federal Circuit's *Dow Chemical* decision. First, as disclosed in the '998 patent, and as agreed by the all experts during the colloquy, a yeast cell entirely free of GPD or GPP will not produce glycerol, thereby satisfying claim 1. Admittedly, there is still the question of what constitutes a "reduction" in GPD or GPP activity, made more problematic by the aerobic (GPD1 and GPP1) and anaerobic (GPD2 and GPP2) forms of each. On the other hand, there is nothing inherently indefinite about the requirement that there be "reduced" activity. In fact, as noted, the defendants claim just that in their marketing materials to the ethanol-producing industry. Moreover, as the United States Supreme Court explained in *Nautilus*, "[s]ome modicum of uncertainty" is allowed. 116 S.Ct. at 2128. Unlike the issues confronting the Supreme Court in *Nautilus* or the Federal Circuit in *Dow Chemical*, the requirement of a reduction is not clearly or convincingly indefinite.<sup>27</sup> As defendants have had an opportunity to respond to plaintiffs' opposition, and because the court has determined that the patent is not indefinite, summary judgment will be granted in plaintiffs' favor on this defense. *See* Fed. R. Civ. P. 56(f); *Ellis v. DHL Express Inc. (USA)*, 633 F.3d 522, 529 (7th Cir. 2011).

### III. Infringement

Because the required proof of infringement of the elements in claim 1 of the '998 patent are largely not in dispute, the resolution of defendants' second basis for seeking summary

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<sup>27</sup> As discussed in the next section, this is not to minimize the burden on the plaintiffs to prove infringement, since at minimum they must prove that a reduction in glycerol results from practicing the '998 patent "as compared to corresponding wild-type cells," something that would likely only be possible to determine by the accused infringer or at least with its cooperation. Of course, the obvious resolution of the infringement dispute would be for the parties to agree to batch runs of the accused products and corresponding wild-type cells, in consultation with the court's neutral expert witness if necessary.

judgment is much more straightforward. A person infringes a patent when she “without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent.” 35 U.S.C. § 271(a). Analysis of patent infringement is a two-step process:

first, the scope of the claims are determined as a matter of law, and second, the properly construed claims are compared to the allegedly infringing device to determine, as a matter of fact, whether all of the limitations of at least one claim are present, either literally or by a substantial equivalent, in the accused device.

*Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1323 (Fed. Cir. 2002); *see also Split Pivot, Inc. v. Trek Bicycle Corp.*, 987 F. Supp. 2d 838, 876 (W.D. Wis. 2013) (explaining that following claims construction, “the claim as properly construed must be compared to the accused device or process”).

Whether an accused product infringes -- literally or by substantial equivalent -- is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998); *TechSearch, L.L.C. v. Intel Corp.*, 286 F.3d 1360, 1370-71 (Fed. Cir. 2002). “Summary judgment is appropriate when it is apparent that only one conclusion as to infringement could be reached by a reasonable jury.” *TechSearch*, 286 F.3d at 1369 (citing *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 540 (Fed. Cir. 1998)). Accordingly, an accused infringer is entitled to summary judgment of noninfringement “where the patent owner’s proof is deficient in meeting an essential part of the legal standard for infringement, since such failure will render all other facts immaterial.” *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1323 (Fed. Cir. 2001) (citing *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1537 (Fed. Cir. 1991)); *see also Bai*, 160 F.3d at 1353 (“[A] literal infringement issue is properly decided upon summary judgment when no genuine issue of material fact exists, in particular, when no reasonable jury could find that every limitation recited in the properly construed claim either is or is not found in the accused

device.” (internal citation omitted)). Concomitantly, the patent owner must provide more than simply “general assertions of facts, general denials, and conclusory statements”; rather, it “must point to an evidentiary conflict created on the record.” *TechSearch*, 286 F.3d at 1372.

Here, defendants maintain that the accused products do *not* have reduced NAD-dependent GPD activity compared to corresponding wild-type cells. (Defs.’ Opening Br. (dkt. #64) 22-25.) Specifically, defendants argue that if the court adopted their proposed meaning of “activity” -- that it is “the expression of GPD” -- they are entitled to summary judgment because: (1) plaintiffs provide “conclusory expert opinions, and no evidence, that the accused products exhibit decreased expression of [GPD] compared to wild-type yeast cells”; and (2) defendants’ testing -- using the Blomberg enzyme activity assay described in the ’998 patent - - “confirms that the accused products exhibit increased expression of [GPD] compared to wild-type yeast cells.” (*Id.* at 22-23 (emphasis in original).)

In their opposition brief, and again at the expert colloquy, plaintiffs argue that if the court adopts their proposed constructions, there is no question that the accused products infringe, such that it is entitled to summary judgment. (Pls.’ Opp’n (dkt. #74) 36.) Plaintiffs further argue that they have put forward enough evidence to establish infringement and have raised serious questions about the “validity, reliability, and credibility of [Lallemand’s GPD activity assays].” (*Id.*) Professor Stephanopoulos’s expert opinion that “a yeast cell that has been engineered to eliminate expression of Gpd2 and that also reportedly exhibits a 30% reduction in glycerol synthesis -- like the Accused Products -- necessarily has reduced Gpd activity compared to the corresponding wild-type strain” is not “conclusory,” as defendants argue. Rather, it derives from “fundamental principles of enzyme kinetics and metabolic engineering” and appears “confirmed by Lallemand’s own business records.” (*Id.* at 37.)

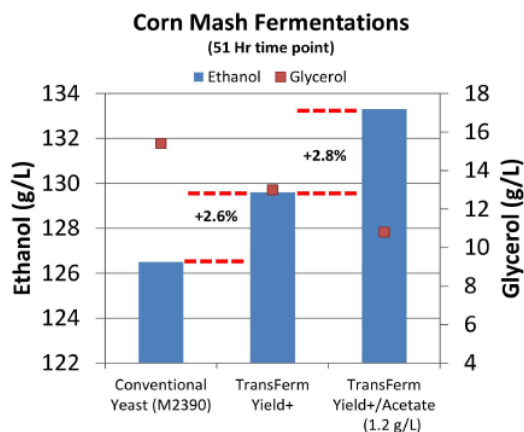
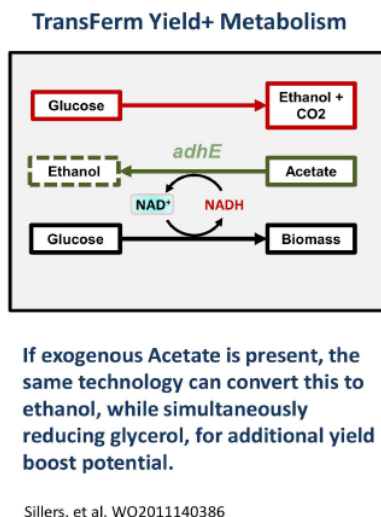
Indeed, plaintiffs rely on Lallemand's internal and advertising documents that appear to tout TFY+ for: (1) having a "[d]own-regulated glycerol pathway" with "down-regulation of GPD1/GPD2"; and (2) reducing glycerol production "primarily by downregulating the gpd1/gpd2 genes." As plaintiffs note, Lallemand's International Patent Publication defines "downregulated" as "mean[ing] decreased in activity, e.g., decreased in enzymatic activity of the enzyme as compared to activity in a native host organism." (*Id.* at 37-38 (quoting WO 2012/138942).) At minimum, these seeming admissions make defendants' denials ring hollow.

Ironically for plaintiffs, it appears most of the statements on which they rely are based on the same dubious use of Blomberg assays that plaintiffs so persuasively attack. (Pls. Opp'n (dkt. #74) 39-42.) Moreover, plaintiffs and their expert have done *no* testing of the accused products to determine whether in fact they are free of any NAD-dependent GPD activity or, at least, have reduced such activity compared to corresponding wild-type cells.

Even accounting for Professor Alper's credible opinion that this would almost certainly be true as a matter of basic science, he conceded at the expert colloquy at least the possibility that a yeast cell that does not express GPD2 might be altered sufficiently so that glycerol production might occur at a level approaching, if not exceeding, that of its corresponding wild-type cell. And defendants have produced some evidence to permit a reasonable jury to find that the accused products have been sufficiently altered to make any reduction in glycerol production unrelated to the elimination of GPD as compared to corresponding wild cells.

Of course, the opposite is also true. Indeed, on the facts provided at summary judgment and in the experts' opinions, there would appear to be a much greater likelihood that a reasonable jury would find infringement. Indeed, Lallemand's own document appears to show that the elimination of GPD2 expression has sufficiently altered the GPD enzyme activity to

appreciably change glycerol production compared to conventional yeast cells:



(TransFerm Yield+ Marketing document (dkt. #47-56) 2.) Defendants may successfully argue at trial that the accused products’ performance is no longer comparable to the “TransFerm Yield+ Metabolism” set forth above, but they are certainly not entitled to summary judgment on infringement. *See TechSearch, L.L.C. v. Intel Corp.*, 286 F.3d 1360, 1370 (Fed. Cir. 2002) (“Summary judgment is appropriate when it is apparent that only one conclusion as to infringement could be reached by a reasonable jury.” (citing *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 540 (Fed. Cir. 1998))). Because of the factual disputes outlined above, neither are plaintiffs.

## ORDER

IT IS ORDERED that:

- 1) The disputed terms are construed as set forth above;
- 2) plaintiffs’ motion for partial summary judgment on defendants’ anticipation defense (dkt. #58) is GRANTED;
- 3) defendants’ motion for summary judgment as to indefiniteness (dkt. #61) is DENIED, and plaintiffs are GRANTED summary judgment on this defense; and

- 4) the parties' cross-requests for summary judgment on noninfringement (dkt. ##61, 74) are DENIED.

Entered this 22nd day of March, 2018.

BY THE COURT:

/s/

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WILLIAM M. CONLEY  
District Judge